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Risk Prediction Models for Out-of-Hospital Cardiac Arrest Outcomes in England

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ABSTRACT

Introduction: The Out-of-Hospital Cardiac Arrest (OHCA) Outcomes project is a national research registry. One of its aims is to explore sources of variation in OHCA survival outcomes. This study reports the development and validation of risk prediction models for return of spontaneous circulation (ROSC) at hospital handover and survival to hospital discharge.

Methods and results: The study included OHCA patients who were treated during 2014 and 2015 by emergency medical services (EMS) from 7 English National Health Service ambulance services. The 2014 data were used to identify important variables and to develop the risk prediction models, which were validated using the 2015 data. Model prediction was measured by area under the curve (AUC), Hosmer-Lemeshow test, Cox calibration regression and Brier score. All analyses were conducted using mixed effects logistic regression models. Important factors included age, gender, witness/bystander cardiopulmonary resuscitation (CPR) combined, aetiology and initial rhythm. Interaction effects between witness/bystander CPR with gender, aetiology and initial rhythm and between aetiology and initial rhythm were significant in both models. The survival model achieved better discrimination and overall accuracy compared with the ROSC model (AUC=0.86 vs 0.67, Brier score=0.072 vs 0.194, respectively). Calibration tests showed over- and under-estimation for the ROSC and survival models, respectively. A sensitivity analysis individually assessing Index of Multiple Deprivation scores and location in the final models substantially improved overall accuracy with inconsistent impact on discrimination.

Conclusion: Our risk prediction models identified and quantified important pre-EMS intervention factors determining survival outcomes in England. The survival model had excellent discrimination.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a leading cause of cardiac related death in developed countries; only one in ten patients survive to hospital discharge.[1, 2] However, in recent years several countries and regions have made major advances in the improvement of OHCA survival rates: 25% of patients in Stavanger, Norway survived to hospital discharge,[3] 21% in North Holland[4] and 24% in Seattle, USA.[5]

In England, there are approximately 80,000 OHCA incidents annually, with resuscitation attempted in less than half by emergency medical services (EMS).[6] However, survival outcomes have shown limited improvement, with data from English ambulance services indicating one in four patients have return of spontaneous circulation (ROSC) sustained to hospital handover, while the survival to hospital discharge rate is still around 10%,[6, 7] with regional variation reported between 2%-12%.[8] A validated risk adjustment model would aid understanding of regional variations, enabling unbiased comparisons between ambulance services for survival outcomes.[9] Risk adjustment models are an important element to support healthcare quality improvement e.g. for in-hospital cardiac arrest (IHCA).[10] Improving the management of OHCA is part of the National Health Service (NHS) Long Term plan[11] and the British Heart Foundation, Resuscitation Council (UK) and NHS England are committed to improving survival from OHCA in England.[12, 13]

Recent studies have recognised a range of OHCA patient case-mix and pre-EMS intervention factors in non-UK populations that are associated with survival. These include: OHCA location;[14, 15] patient age, gender;[14, 16-19] witnessed status; bystander cardiopulmonary resuscitation (CPR);[14, 16, 19, 20] initial rhythm;[14, 17, 19] aetiology;[14] public access defibrillator (PAD) use;[16] and socioeconomic status.[21, 22]

The relative contribution of each of these factors to survival varies between countries. Only a few studies have assessed the possible interaction between pre-EMS intervention factors and OHCA outcomes in a systematic process through the development and validation of risk prediction models.[23, 24] However, such models also include EMS intervention factors. Whilst validated models to risk-adjust survival rates for IHCA exist,[10] no such models have currently been developed for OHCA outcomes in England.

The aim of this analysis was to 1) identify key factors associated with two survival outcomes, ROSC at hospital handover and survival to hospital discharge; 2) develop and evaluate models to predict both outcomes in England; and 3) support quality improvement activities in the UK to improve OHCA outcomes.

Data and Methods

Data source

The Out-of-hospital Cardiac Arrest Outcomes (OHCAO) registry, hosted by the University of Warwick, is a national research database developed in accordance with Utstein-style guidelines.[25] UK ambulance services collect and contribute OHCA cases where there is a resuscitation attempt by EMS. Patient case-mix data, process variables, structure data and survival outcomes are collected. Details of the project have been published elsewhere.[26]

Study population

The study population included OHCA cases from 1st January 2014 to 31st December 2015 treated by 7 out of 10 English NHS ambulance services providing data to the registry. Patients of all age groups were included except those with a Do Not Attempt Resuscitation order in place or who achieved ROSC before EMS arrival. The 2014 data were used to identify important factors of the outcomes and develop the prediction models. The 2015 data were used for model validation.

Data management

Variables assessed in the analysis included age, gender, witnessed status, bystander CPR, aetiology and initial rhythm (Table 1). Age was used as a continuous variable in the analysis. For aetiology, unknown cause was presumed as medical according to the Utstein definitions.[25] We merged categories with few cases to enable better estimation. The aetiology was re-defined as 1) medical; 2) trauma and exsanguination; 3) overdose, asphyxia, and submersion; 4) other. Similarly, the rhythm for modelling included 1) ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT); 2) asystole; 3) pulseless electrical activity (PEA) and bradycardia. Cases that had one or more missing assessed variables were excluded from the analysis.

Bystander CPR has been widely accepted as a key factor for improving survival.[12, 27] In our data, patients witnessed by EMS are treated as not receiving bystander CPR. However, they are different from the non-EMS witnessed patients in terms of the time to start of CPR and advanced treatments, and therefore in their chance of survival.[28] Consequently, the combination of these witnessed cases may cancel out the bystander CPR effect. Therefore, the witness and bystander CPR were assessed as an interaction using the following categories: 1) unwitnessed and no bystander CPR; 2) unwitnessed but bystander CPR given; 3) EMS witnessed; 4) bystander witnessed but no CPR given; 5) bystander witnessed and CPR given. Witnessed cases with unspecified type (by bystander or EMS) were excluded from the analysis to improve the accuracy of the analysis.

Because of the heterogeneity in data collection methods across the UK, ambulance services provided data of varying quality. Particularly, post-hospital transfer data collection is complex and expensive, leading to variation in levels of missing data. Large amount of missing data in a number of the assessed variables and outcomes resulted in excluding four of the ten ambulance services from model development. However, only three of the four ambulance services were excluded from model validation for the same reason. Ethnicity and public access defibrillation (PAD) use were not included in the analysis due to consistently poor data quality across the registry. The Index of Multiple Deprivation (IMD) scores were extracted from the English indices of deprivation data via the linkage to the patients' home postcode. The OHCA location data were converted from addresses to postcodes before being recoded to home or non-home by comparing the location postcode with home postcode. The 2014 location data had less missing data due to a data quality improvement project in collaboration with Public Health England, which was not available for 2015 data collection. The IMD and location were assessed in the final models as a sensitivity analysis to explore their contribution to the prediction improvement.

Statistical methods

Factors and outcomes were summarised in the following way: frequency and proportion for categorical variables and mean and standard deviation (SD) for continuous variables. Assessment and estimation were carried out using mixed effects logistic regression models. Ambulance services were fitted as a random effect in all models to account for the potential heterogeneity of patient and event characteristics across ambulance services. The key factors were determined if they showed statistical significance ($p<0.05$) when individually tested in a mixed effects model.

We employed the fractional polynomial (FP) method to explore the best fitting functional form of continuous factors using linear and polynomial functions.[29] As the method does not take into account the random effect, we decided that the best form would only be used if it also improved model fit in the mixed effects models. Otherwise, only the linear form was included.

The development of the prediction models for each outcome were conducted in three stages (Figure 1).

Model performance was measured by model fit as well as prediction performance (discrimination and calibration). How well the model fit the data was measured by Akaike information criterion (AIC) value. AIC estimates the relative amount of information lost by a given model: the lower the AIC value, the less information a model loses, the higher the quality of that model. Model discrimination (the ability of the model to separate individuals who do and do not achieve sustained ROSC or survive) was quantified by the area under the receiver operating characteristic curve (AUC) with 95% confidence interval, which measures how well the prediction can discriminate positive and negative outcomes.[30] The following categories were used to interpret AUC: 1) ≥0.9 = outstanding; 2) 0.8-0.9 = excellent; 3) 0.7-0.8 = acceptable, 4) <0.7 = poor.[31] A range of measures were taken to evaluate model calibration (i.e. the agreement between observed and predicted risk). 1) Hosmer-Lemeshow test compares the agreement between observed and predicted values. However, the test is sensitive to the sample size.[31] Hence, the observed proportion of positive outcomes (e.g. survival) were plotted against the deciles of the predicted values for a virtual inspection. 2) Cox calibration fits a line between the outcome and log odds of the prediction using logistic regression.[32] A line with an intercept of 0 and slope of 1 indicates perfect agreement. 3) Overall accuracy was measured by Brier's score, the mean squared error of prediction with 0 indicating the best prediction.[33] The developed models were applied in the validation data to obtain the predictions and the model performance measurements.

A p-value <0.05 was considered statistically significant. The FP method was applied in Stata v15 (StataCorp). Other analyses were carried out in SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

Results

There were 17,528 and 17,078 eligible OHCA cases in 2014 and 2015, respectively. By excluding missing outcome data, 16,470 and 10,648 cases were used for the model development of ROSC at handover and survival to discharge, respectively; and 16,319 and

13,686 cases were used to validate models, respectively. Patient level characteristics and study outcomes in both development and validation sets are summarised in Table 1.

Key factors of outcomes

Individual assessment of candidate factors is summarised in Table 1. Gender, witness/bystander CPR, aetiology and initial rhythm were significantly associated with both outcomes. Age was significantly associated only with survival to hospital discharge. IMD scores and location data were available in less than half of the development data. Only location was significantly associated with both outcomes (Table 2).

Model development

At stage 1, all individually significant factors remained in Model S1 for ROSC at handover and survival to discharge (Table 3). These full models had the best model fit and prediction performance at this stage (Table 4).

Fewer interaction terms were evaluated at stage 2 for ROSC compared with survival to hospital discharge (Table 3). Four interaction terms with p-value<0.1 were included for further analysis in Model S2 for both outcomes: witness/bystander CPR with gender, aetiology and initial rhythm, and aetiology with initial rhythm.

For both outcomes, all included interactions and main effects from the corresponding Model S2 remained significant and produced the best prediction performance at stage 3. Therefore, Model S3 is identical to Model S2 for both outcomes. In the ROSC Model S3, the main effect of witness/bystander CPR was not significant but remained in the final model mainly due to its clinical importance. Additionally, the removal of this term led to a negligible decrease in the model fit (AIC from 18050.2 to 18051.0) and had no benefit gained regarding the AUC and brier score (Appendix Table 1). Likewise, gender was kept in the survival Model S3 for the same reason (AIC changed from 6208.8 to 6208.9 after removal). The Model S3 for both outcomes were decided as the final models. The fully specification of each models are shown in Table 3.

Model validation

The results of the validation of Model S3 for both OHCA outcomes are shown in Table 4. The AUC values showed that the survival model produced good prediction (AUC=0.85 in development and 0.87 in validation) while the ROSC model was less so (AUC=0.70 in development and 0.67 in validation). The Cox calibration regression produced a positive intercept and a slope<1 in the validation data for the ROSC model, indicating a decreasing underestimation. The survival model, however, had a negative intercept, indicating a consistent overestimation of the survival rate. These trends were also supported by the calibration plots (Figure 2).

Sensitivity analysis

The IMD 2010 and 2015 scores substantially improved the AUC in the development (0.69 to 0.77 for ROSC at handover, 0.85 to 0.89 for survival at discharge) but not in the validation data (0.66 to 0.67 for ROSC at handover, 0.87 to 0.83 for survival at discharge). Consistent improvement was gained in terms of the overall accuracy for both outcomes in the development and validation data. However, the Cox calibration intercept and slope indicated the inclusion of these variables led to more over-/under-estimations for individual cardiac arrest patients. The impact of location was inconclusive as both models had worse performance. It may be caused by more missing data in the validation data but requires further analysis.

Discussion

In this analysis we developed and validated risk prediction models for ROSC at hospital handover and survival to hospital discharge using the 2014 and 2015 OHCAO data, respectively, of 7 English ambulance services. Gender, aetiology, witness, bystander CPR and initial rhythm were used as the key factors for both outcomes, together with their first-order interactions. Age was an additional factor included in the survival model. The survival model had an excellent predictive performance with an AUC of 0.87 in the validation data, while more improvement is needed for the ROSC model with an AUC of 0.67.

Our model development was based on the case-mix and event data prior to EMS intervention. The data depict the initial status of an OHCA patient. Case-mix data are commonly used to account for the variability of outcomes in healthcare research.[34] Early recognition and access to EMS service, as well as early CPR, are fundamental to and the strongest links[35] of improving OHCA outcomes in the chain of survival.[36]

Age had a less significant effect on ROSC at hospital handover than on survival to hospital discharge. Previous studies have demonstrated a conflicting result of the age effect. Some recent studies showed a significant association[14, 37] but others reported the opposite result.[38, 39] In addition, in a study of non-trauma Welsh OHCA patients, Barnard et al identified a significant quadratic (i.e. squared) effect but not linear effect of age.[40]

The survival model had better discrimination and overall accuracy compared with the ROSC model. Event location and socioeconomic status, measured by IMD 2010 and 2015 score, are associated with survival outcomes.[14, 15, 21, 22] However, the inclusion of these data in the sensitivity analysis only yielded a small improvement in AUC and Brier score for both models and did not reduce the model performance gap. The ROSC after cardiac arrest (RACA) score, which was developed in a similar way to our model S1 with the inclusion of the time to EMS arrival, achieved an AUC of 0.73.[14] The model discrimination was relatively improved but is still not as good as our survival model. The large prediction discrepancy between ROSC and survival models suggested that the pre-EMS intervention variables may not be the best candidates for predicting ROSC. Sustained ROSC at hospital transfer is a short-term survival event. It is associated with EMS intervention factors, such as CPR quality,[41] airway management[42] and drug treatment.[43] Inclusion of EMS intervention factors in the model may further improve performance.

Our survival model had excellent predictive performance when compared with the existing models for non-UK populations. Valenzuela et al developed a model using age, bystander CPR, time to CPR, time to defibrillation and time related interactions in the US patients.[44] The model made poor predictions of survival (AUC=0.66). A Dutch study also assessed survival prediction using three cumulative sets of data related to bystander, first responder and paramedics. The first responder model also looked at pre-EMS intervention data and had similar model discrimination (AUC=0.85) to that of our model. The other two, involving less and more predictors, had an AUC of 0.76 and 0.90, respectively.[45] The French OHCA score was developed using rhythm, time to CPR, CPR duration and laboratory data.[46] This tool produced an AUC of 0.88 when restricting the prediction of survival with good neurological outcome in a small group of patients achieving ROSC. It was further developed as the Cardiac Arrest Hospital Prognosis (CAHP) score which achieved an AUC of 0.85 and 0.91 in two larger validation sets.[15] However, both scores were inferior to the Swedish risk score in terms of AUC (0.75 for OHCA and CAHP vs 0.84) when three models were validated using the Target Temperature Management trial data.[47]

Implications

Improving OHCA management and survival in England is advocated in key national documents.[11, 13] Our risk prediction models identified important pre-EMS intervention factors of survival outcomes in England. The models could provide case-mix adjusted performance evaluation for the NHS ambulance services. More importantly, we aim to use the models to identify at-risk patients in the English population, help ambulance services and health authorities develop health strategies in different communities, and ultimately improve survival rates and reduce the health burden of OHCA.

Strengths and limitations

This is the first analysis to develop and evaluate risk prediction models for OHCA survival outcomes in the UK. It gained strength by using the OHCAO registry data. This national registry collects and standardises a key sub-set of Utstein elements[48] from the participating UK ambulance services. Thus, the models offer comparable results across the ambulance services and can be applicable to other registries built on the same guidelines. In addition, we used mixed effect logistic regression to carry out the analysis. The random effect model takes into account the heterogeneity of patient and event characteristics across ambulance services and provides more precise estimations.

This analysis also has several limitations. We did not include several pre- and peri-EMS intervention variables that were used as factors of OHCA survival outcomes in other models due to the perspective of our analysis and the limited Utstein elements. For example, prodromal symptoms[18] and biomarkers[49] were not collected in the OHCAO registry. However, in the future data linkage may enable us to evaluate their contribution in a more comprehensive prediction model. Our datasets contained data of varying quality because of the heterogeneous data collection processes across ambulance services. Some important variables, such as OHCA location and socioeconomic status, had more missing data and were restricted to the sensitivity analysis to avoid compromising the model interpretation and prediction. However, some improvement has been observed, such as less missing survival data from 2014 to 2015. Ongoing work to improve the data quality should enable improvement in model performance. In addition, location did not improve the model performance in the sensitivity analysis. The effect could have become irrelevant after the inclusion of other prediction terms. The improvement of data quality may allow better assessment of the variable.

Conclusion

In conclusion, our risk prediction models identified and quantified important pre-EMS intervention factors determining survival outcomes in England. The survival model had excellent discrimination.

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Out-of-Hospital Cardiac Arrest Outcomes Steering Committee

Conflict of interest statement

Chen Ji, Terry Brown, Scott Booth, Claire Hawkes and Gavin Perkins are employed by the University of Warwick, which receives grants from the British Heart Foundation and the Resuscitation Council (UK) for the conduct of the OHCAO project. Jerry Nolan, James Mapstone, Rachael T Fothergill, Robert Spaight, and Sarah Black report no conflicts of interest.

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Risk Prediction Models for Out-of-Hospital Cardiac Arrest Outcomes in England

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ABSTRACT

Introduction: The Out-of-Hospital Cardiac Arrest (OHCA) Outcomes project is a national research registry. One of its aims is to explore sources of variation in OHCA survival outcomes. This study reports the development and validation of risk prediction models for return of spontaneous circulation (ROSC) at hospital handover and survival to hospital discharge.

Methods and results: The study included OHCA patients who were treated during 2014 and 2015 by emergency medical services (EMS) from 7 English National Health Service ambulance services. The 2014 data were used to identify important variables and to develop the risk prediction models, which were validated using the 2015 data. Model prediction was measured by area under the curve (AUC), Hosmer-Lemeshow test, Cox calibration regression and Brier score. All analyses were conducted using mixed effects logistic regression models. Important factors included age, gender, witness/bystander cardiopulmonary resuscitation (CPR) combined, aetiology and initial rhythm. Interaction effects between witness/bystander CPR with gender, aetiology and initial rhythm and between aetiology and initial rhythm were significant in both models. The survival model achieved better discrimination and overall accuracy compared with the ROSC model (AUC=0.86 vs 0.67, Brier score=0.072 vs 0.194, respectively). Calibration tests showed over- and under-estimation for the ROSC and survival models, respectively. A sensitivity analysis individually assessing Index of Multiple Deprivation scores and location in the final models substantially improved overall accuracy with inconsistent impact on discrimination.

Conclusion: Our risk prediction models identified and quantified important pre-EMS intervention factors determining survival outcomes in England. The survival model had excellent discrimination.

Introduction

Out-of-hospital cardiac arrest (OHCA) is a leading cause of cardiac related death in developed countries; only one in ten patients survive to hospital discharge.[1, 2] However, in recent years several countries and regions have made major advances in the improvement of OHCA survival rates: 25% of patients in Stavanger, Norway survived to hospital discharge,[3] 21% in North Holland[4] and 24% in Seattle, USA.[5]

In England, there are approximately 80,000 OHCA incidents annually, with resuscitation attempted in less than half by emergency medical services (EMS).[6] However, survival outcomes have shown limited improvement, with data from English ambulance services indicating one in four patients have return of spontaneous circulation (ROSC) sustained to hospital handover, while the survival to hospital discharge rate is still around 10%,[6, 7] with regional variation reported between 2%-12%.[8] A validated risk adjustment model would aid understanding of regional variations, enabling unbiased comparisons between ambulance services for survival outcomes.[9] Risk adjustment models are an important element to support healthcare quality improvement e.g. for in-hospital cardiac arrest (IHCA).[10] Improving the management of OHCA is part of the National Health Service (NHS) Long Term plan[11] and the British Heart Foundation, Resuscitation Council (UK) and NHS England are committed to improving survival from OHCA in England.[12, 13]

Recent studies have recognised a range of OHCA patient case-mix and pre-EMS intervention factors in non-UK populations that are associated with survival. These include: OHCA location;[14, 15] patient age, gender;[14, 16-19] witnessed status; bystander cardiopulmonary resuscitation (CPR);[14, 16, 19, 20] initial rhythm;[14, 17, 19] aetiology;[14] public access defibrillator (PAD) use;[16] and socioeconomic status.[21, 22]

The relative contribution of each of these factors to survival varies between countries. Only a few studies have assessed the possible interaction between pre-EMS intervention factors and OHCA outcomes in a systematic process through the development and validation of risk prediction models.[23, 24] However, such models also include EMS intervention factors. Whilst validated models to risk-adjust survival rates for IHCA exist,[10] no such models have currently been developed for OHCA outcomes in England.

The aim of this analysis was to 1) identify key factors associated with two survival outcomes, ROSC at hospital handover and survival to hospital discharge; 2) develop and evaluate models to predict both outcomes in England; and 3) support quality improvement activities in the UK to improve OHCA outcomes.

Data and Methods

Data source

The Out-of-hospital Cardiac Arrest Outcomes (OHCAO) registry, hosted by the University of Warwick, is a national research database developed in accordance with Utstein-style guidelines.[25] UK ambulance services collect and contribute OHCA cases where there is a resuscitation attempt by EMS. Patient case-mix data, process variables, structure data and survival outcomes are collected. Details of the project have been published elsewhere.[26]

Study population

The study population included OHCA cases from 1st January 2014 to 31st December 2015 treated by 7 out of 10 English NHS ambulance services providing data to the registry. Patients of all age groups were included except those with a Do Not Attempt Resuscitation order in place or who achieved ROSC before EMS arrival. The 2014 data were used to identify important factors of the outcomes and develop the prediction models. The 2015 data were used for model validation.

Data management

Variables assessed in the analysis included age, gender, witnessed status, bystander CPR, aetiology and initial rhythm (Table 1). Age was used as a continuous variable in the analysis. For aetiology, unknown cause was presumed as medical according to the Utstein definitions.[25] We merged categories with few cases to enable better estimation. The aetiology was re-defined as 1) medical; 2) trauma and exsanguination; 3) overdose, asphyxia, and submersion; 4) other. Similarly, the rhythm for modelling included 1) ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT); 2) asystole; 3) pulseless electrical activity (PEA) and bradycardia. Cases that had one or more missing assessed variables were excluded from the analysis.

Bystander CPR has been widely accepted as a key factor for improving survival.[12, 27] In our data, patients witnessed by EMS are treated as not receiving bystander CPR. However, they are different from the non-EMS witnessed patients in terms of the time to start of CPR and advanced treatments, and therefore in their chance of survival.[28] Consequently, the combination of these witnessed cases may cancel out the bystander CPR effect. Therefore, the witness and bystander CPR were assessed as an interaction using the following categories: 1) unwitnessed and no bystander CPR; 2) unwitnessed but bystander CPR given; 3) EMS witnessed; 4) bystander witnessed but no CPR given; 5) bystander witnessed and CPR given. Witnessed cases with unspecified type (by bystander or EMS) were excluded from the analysis to improve the accuracy of the analysis.

Because of the heterogeneity in data collection methods across the UK, ambulance services provided data of varying quality. Particularly, post-hospital transfer data collection is complex and expensive, leading to variation in levels of missing data. Large amount of missing data in a number of the assessed variables and outcomes resulted in excluding four of the ten ambulance services from model development. However, only three of the four ambulance services were excluded from model validation for the same reason. Ethnicity and public access defibrillation (PAD) use were not included in the analysis due to consistently poor data quality across the registry. The Index of Multiple Deprivation (IMD) scores were extracted from the English indices of deprivation data via the linkage to the patients' home postcode. The OHCA location data were converted from addresses to postcodes before being recoded to home or non-home by comparing the location postcode with home postcode. The 2014 location data had less missing data due to a data quality improvement project in collaboration with Public Health England, which was not available for 2015 data collection. The IMD and location were assessed in the final models as a sensitivity analysis to explore their contribution to the prediction improvement.

Statistical methods

Factors and outcomes were summarised in the following way: frequency and proportion for categorical variables and mean and standard deviation (SD) for continuous variables. Assessment and estimation were carried out using mixed effects logistic regression models. Ambulance services were fitted as a random effect in all models to account for the potential heterogeneity of patient and event characteristics across ambulance services. The key factors were determined if they showed statistical significance ($p<0.05$) when individually tested in a mixed effects model.

We employed the fractional polynomial (FP) method to explore the best fitting functional form of continuous factors using linear and polynomial functions.[29] As the method does not take into account the random effect, we decided that the best form would only be used if it also improved model fit in the mixed effects models. Otherwise, only the linear form was included.

The development of the prediction models for each outcome were conducted in three stages (Figure 1).

Model performance was measured by model fit as well as prediction performance (discrimination and calibration). How well the model fit the data was measured by Akaike information criterion (AIC) value. AIC estimates the relative amount of information lost by a given model: the lower the AIC value, the less information a model loses, the higher the quality of that model. Model discrimination (the ability of the model to separate individuals who do and do not achieve sustained ROSC or survive) was quantified by the area under the receiver operating characteristic curve (AUC) with 95% confidence interval, which measures how well the prediction can discriminate positive and negative outcomes.[30] The following categories were used to interpret AUC: 1) ≥0.9 = outstanding; 2) 0.8-0.9 = excellent; 3) 0.7-0.8 = acceptable, 4) <0.7 = poor.[31] A range of measures were taken to evaluate model calibration (i.e. the agreement between observed and predicted risk). 1) Hosmer-Lemeshow test compares the agreement between observed and predicted values. However, the test is sensitive to the sample size.[31] Hence, the observed proportion of positive outcomes (e.g. survival) were plotted against the deciles of the predicted values for a virtual inspection. 2) Cox calibration fits a line between the outcome and log odds of the prediction using logistic regression.[32] A line with an intercept of 0 and slope of 1 indicates perfect agreement. 3) Overall accuracy was measured by Brier's score, the mean squared error of prediction with 0 indicating the best prediction.[33] The developed models were applied in the validation data to obtain the predictions and the model performance measurements.

A p-value <0.05 was considered statistically significant. The FP method was applied in Stata v15 (StataCorp). Other analyses were carried out in SAS v9.4 (SAS Institute Inc., Cary, NC, USA).

Results

There were 17,528 and 17,078 eligible OHCA cases in 2014 and 2015, respectively. By excluding missing outcome data, 16,470 and 10,648 cases were used for the model development of ROSC at handover and survival to discharge, respectively; and 16,319 and

13,686 cases were used to validate models, respectively. Patient level characteristics and study outcomes in both development and validation sets are summarised in Table 1.

Key factors of outcomes

Individual assessment of candidate factors is summarised in Table 1. Gender, witness/bystander CPR, aetiology and initial rhythm were significantly associated with both outcomes. Age was significantly associated only with survival to hospital discharge. IMD scores and location data were available in less than half of the development data. Only location was significantly associated with both outcomes (Table 2).

Model development

At stage 1, all individually significant factors remained in Model S1 for ROSC at handover and survival to discharge (Table 3). These full models had the best model fit and prediction performance at this stage (Table 4).

Fewer interaction terms were evaluated at stage 2 for ROSC compared with survival to hospital discharge (Table 3). Four interaction terms with p-value<0.1 were included for further analysis in Model S2 for both outcomes: witness/bystander CPR with gender, aetiology and initial rhythm, and aetiology with initial rhythm.

For both outcomes, all included interactions and main effects from the corresponding Model S2 remained significant and produced the best prediction performance at stage 3. Therefore, Model S3 is identical to Model S2 for both outcomes. In the ROSC Model S3, the main effect of witness/bystander CPR was not significant but remained in the final model mainly due to its clinical importance. Additionally, the removal of this term led to a negligible decrease in the model fit (AIC from 18050.2 to 18051.0) and had no benefit gained regarding the AUC and brier score (Appendix Table 1). Likewise, gender was kept in the survival Model S3 for the same reason (AIC changed from 6208.8 to 6208.9 after removal). The Model S3 for both outcomes were decided as the final models. The fully specification of each models are shown in Table 3.

Model validation

The results of the validation of Model S3 for both OHCA outcomes are shown in Table 4. The AUC values showed that the survival model produced good prediction (AUC=0.85 in development and 0.87 in validation) while the ROSC model was less so (AUC=0.70 in development and 0.67 in validation). The Cox calibration regression produced a positive intercept and a slope<1 in the validation data for the ROSC model, indicating a decreasing underestimation. The survival model, however, had a negative intercept, indicating a consistent overestimation of the survival rate. These trends were also supported by the calibration plots (Figure 2).

Sensitivity analysis

The IMD 2010 and 2015 scores substantially improved the AUC in the development (0.69 to 0.77 for ROSC at handover, 0.85 to 0.89 for survival at discharge) but not in the validation data (0.66 to 0.67 for ROSC at handover, 0.87 to 0.83 for survival at discharge). Consistent improvement was gained in terms of the overall accuracy for both outcomes in the development and validation data. However, the Cox calibration intercept and slope indicated the inclusion of these variables led to more over-/under-estimations for individual cardiac arrest patients. The impact of location was inconclusive as both models had worse performance. It may be caused by more missing data in the validation data but requires further analysis.

Discussion

In this analysis we developed and validated risk prediction models for ROSC at hospital handover and survival to hospital discharge using the 2014 and 2015 OHCAO data, respectively, of 7 English ambulance services. Gender, aetiology, witness, bystander CPR and initial rhythm were used as the key factors for both outcomes, together with their first-order interactions. Age was an additional factor included in the survival model. The survival model had an excellent predictive performance with an AUC of 0.87 in the validation data, while more improvement is needed for the ROSC model with an AUC of 0.67.

Our model development was based on the case-mix and event data prior to EMS intervention. The data depict the initial status of an OHCA patient. Case-mix data are commonly used to account for the variability of outcomes in healthcare research.[34] Early recognition and access to EMS service, as well as early CPR, are fundamental to and the strongest links[35] of improving OHCA outcomes in the chain of survival.[36]

Age had a less significant effect on ROSC at hospital handover than on survival to hospital discharge. Previous studies have demonstrated a conflicting result of the age effect. Some recent studies showed a significant association[14, 37] but others reported the opposite result.[38, 39] In addition, in a study of non-trauma Welsh OHCA patients, Barnard et al identified a significant quadratic (i.e. squared) effect but not linear effect of age.[40]

The survival model had better discrimination and overall accuracy compared with the ROSC model. Event location and socioeconomic status, measured by IMD 2010 and 2015 score, are associated with survival outcomes.[14, 15, 21, 22] However, the inclusion of these data in the sensitivity analysis only yielded a small improvement in AUC and Brier score for both models and did not reduce the model performance gap. The ROSC after cardiac arrest (RACA) score, which was developed in a similar way to our model S1 with the inclusion of the time to EMS arrival, achieved an AUC of 0.73.[14] The model discrimination was relatively improved but is still not as good as our survival model. The large prediction discrepancy between ROSC and survival models suggested that the pre-EMS intervention variables may not be the best candidates for predicting ROSC. Sustained ROSC at hospital transfer is a short-term survival event. It is associated with EMS intervention factors, such as CPR quality,[41] airway management[42] and drug treatment.[43] Inclusion of EMS intervention factors in the model may further improve performance.

Our survival model had excellent predictive performance when compared with the existing models for non-UK populations. Valenzuela et al developed a model using age, bystander CPR, time to CPR, time to defibrillation and time related interactions in the US patients.[44] The model made poor predictions of survival (AUC=0.66). A Dutch study also assessed survival prediction using three cumulative sets of data related to bystander, first responder and paramedics. The first responder model also looked at pre-EMS intervention data and had similar model discrimination (AUC=0.85) to that of our model. The other two, involving less and more predictors, had an AUC of 0.76 and 0.90, respectively.[45] The French OHCA score was developed using rhythm, time to CPR, CPR duration and laboratory data.[46] This tool produced an AUC of 0.88 when restricting the prediction of survival with good neurological outcome in a small group of patients achieving ROSC. It was further developed as the Cardiac Arrest Hospital Prognosis (CAHP) score which achieved an AUC of 0.85 and 0.91 in two larger validation sets.[15] However, both scores were inferior to the Swedish risk score in terms of AUC (0.75 for OHCA and CAHP vs 0.84) when three models were validated using the Target Temperature Management trial data.[47]

Implications

Improving OHCA management and survival in England is advocated in key national documents.[11, 13] Our risk prediction models identified important pre-EMS intervention factors of survival outcomes in England. The models could provide case-mix adjusted performance evaluation for the NHS ambulance services. More importantly, we aim to use the models to identify at-risk patients in the English population, help ambulance services and health authorities develop health strategies in different communities, and ultimately improve survival rates and reduce the health burden of OHCA.

Strengths and limitations

This is the first analysis to develop and evaluate risk prediction models for OHCA survival outcomes in the UK. It gained strength by using the OHCAO registry data. This national registry collects and standardises a key sub-set of Utstein elements[48] from the participating UK ambulance services. Thus, the models offer comparable results across the ambulance services and can be applicable to other registries built on the same guidelines. In addition, we used mixed effect logistic regression to carry out the analysis. The random effect model takes into account the heterogeneity of patient and event characteristics across ambulance services and provides more precise estimations.

This analysis also has several limitations. We did not include several pre- and peri-EMS intervention variables that were used as factors of OHCA survival outcomes in other models due to the perspective of our analysis and the limited Utstein elements. For example, prodromal symptoms[18] and biomarkers[49] were not collected in the OHCAO registry. However, in the future data linkage may enable us to evaluate their contribution in a more comprehensive prediction model. Our datasets contained data of varying quality because of the heterogeneous data collection processes across ambulance services. Some important variables, such as OHCA location and socioeconomic status, had more missing data and were restricted to the sensitivity analysis to avoid compromising the model interpretation and prediction. However, some improvement has been observed, such as less missing survival data from 2014 to 2015. Ongoing work to improve the data quality should enable improvement in model performance. In addition, location did not improve the model performance in the sensitivity analysis. The effect could have become irrelevant after the inclusion of other prediction terms. The improvement of data quality may allow better assessment of the variable.

Conclusion

In conclusion, our risk prediction models identified and quantified important pre-EMS intervention factors determining survival outcomes in England. The survival model had excellent discrimination.

Acknowledgements

Out-of-Hospital Cardiac Arrest Outcomes Steering Committee

Conflict of interest statement

Chen Ji, Terry Brown, Scott Booth, Claire Hawkes and Gavin Perkins are employed by the University of Warwick, which receives grants from the British Heart Foundation and the Resuscitation Council (UK) for the conduct of the OHCAO project. Jerry Nolan, James Mapstone, Rachael T Fothergill, Robert Spaight, and Sarah Black report no conflicts of interest.

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Table 1: Characteristics of OHCA and survival outcomes in the development and validation sets

	2014 (N=17528)	**2015 (N=17078)**
Age - mean (SD)	68.9 (19.0)	68.0 (19.3)
Gender		
Male	10933 (62.4%)	10770 (63.1%)
Female	6595 (37.6%)	6308 (36.9%)
IMD 2010 score - mean (SD)	22.5 (14.9)	24.2 (16.2)
Missing	11054 (63.1%)	7533 (44.1%)
IMD 2015 score - mean (SD)	22.8 (14.9)	24.3 (16.3)
Missing	11054 (63.1%)	7533 (44.1%)
Witnessed by		
Unwitnessed	6569 (37.5%)	5851 (34.3%)
EMS	2835 (16.2%)	3035 (17.8%)
Layperson	8124 (46.3%)	8192 (48.0%)
Bystander CPR		
Yes	8272 (56.3%)	7919 (56.4%)
No	6421 (43.7%)	6124 (43.6%)
Not applicable (EMS witnessed)	2835	3035
Aetiology		
Medical	15486 (88.4%)	14505 (84.9%)
Trauma and Exsanguination	527 (3.0%)	502 (2.9%)
Trauma	527 (3.0%)	501 (2.9%)
Exsanguination	0 (0.0%)	1 (0.0%)
Submersion, overdose, asphyxia and respiratory	637 (3.6%)	695 (4.1%)
Submersion	38 (0.2%)	35 (0.2%)
Drug overdose	65 (0.4%)	232 (1.4%)
Asphyxia	534 (3.0%)	428 (2.5%)
Respiratory	0 (0.0%)	0 (0.0%)
Other (non-cardiac)	878 (5.0%)	1376 (8.1%)
Initial rhythm		
VF/VT	4691 (26.8%)	4143 (24.3%)
Asystole	9067 (51.7%)	8776 (51.4%)
PEA and bradycardia	3770 (21.5%)	4159 (24.4%)
PEA	3660 (20.9%)	4069 (23.8%)
Bradycardia	110 (0.6%)	90 (0.5%)
Location		
Home	6145 (35.1%)	1621 (9.5%)
Non-home	1689 (9.6%)	512 (3.0%)
Missing	9694 (55.3%)	14945 (87.5%)
Survival outcomes		
ROSC at hospital handover		
Yes	4696 (26.8%)	5194 (30.4%)
No	11774 (67.2%)	11125 (65.1%)
Missing	1058 (6.0%)	759 (4.4%)
Survival to hospital discharge		
Yes	1427 (8.1%)	1484 (8.7%)

No	9221 (52.6%)	12202 (71.4%)
Missing	6880 (39.3%)	3392 (19.9%)

Note: Percentages were calculated using the total N in each year as the denominator and may not added up to 100% due to rounding errors. SD, standard deviation; IMD, Index of Multiple Deprivation; EMS, emergency medical services; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation.

Table 2: Association between the included factors and survival outcomes

	ROSC at hospital handover (N=16470)		Survival to hospital discharge (N=10648)	
Variables	Odds ratio (95% CI)	p-value	Odds ratio (95% CI)	p-value
Age	1.002 (0.999, 1.004)	0.068	0.984 (0.981, 0.987)	<0.001
Gender				
Male	1	0.014	1	<0.001
Female	1.091 (1.018, 1.170)		0.606 (0.534, 0.687)	
Witness/bystander CPR				
Unwitnessed and no bystander CPR	1	<0.001	1	<0.001
Unwitnessed but bystander CPR given	0.846 (0.742, 0.965)		1.162 (0.870, 1.553)	
EMS witnessed	2.309 (2.036, 2.618)		4.822 (3.754, 6.195)	
Bystander witnessed but no CPR given	1.764 (1.552, 2.005)		2.000 (1.520, 2.630)	
Bystander witnessed and CPR given	2.112 (1.884, 2.367)		3.001 (2.345, 3.841)	
Aetiology				
Medical	1	0.006	1	<0.001
Trauma and Exsanguination	0.786 (0.639, 0.965)		0.470 (0.303, 0.730)	
Submersion, overdose, asphyxia and respiratory	1.181 (0.991, 1.407)		0.745 (0.541, 1.027)	
Other	0.857 (0.729, 1.008)		0.507 (0.356, 0.722)	
Initial rhythm				
VF/VT	1	<0.001	1	<0.001
Asystole	0.857 (0.729, 1.008)		0.507 (0.356, 0.722)	
PEA and bradycardia	0.247 (0.228, 0.268)		0.068 (0.057, 0.082)	
IMD 2010 score*	1.002 (0.998, 1.006)	0.438	0.999 (0.993, 1.005)	0.689
IMD 2015 score*	1.001 (0.997, 1.005)	0.747	1.000 (0.994, 1.006)	0.912
Location†				
Non-home	1	<0.001	1	<0.001
Home	0.793 (0.704, 0.893)		0.510 (0.429, 0.607)	

*Note: *, only 6383 and 4214 cases included in the ROSC and survival analysis, respectively; †, only 7107 and 3996 cases included in the ROSC and survival analysis, respectively.*

Table 3: Model specification for Stages 1, 2 and 3.

Model		**Outcome**	**Factors**
Stage 1	S1 (ROSC)	ROSC at hospital handover	gender + witness/bystander CPR + aetiology + initial rhythm
	S1 (Survival)	Survival to hospital discharge	age + gender + witness/bystander CPR + aetiology + initial rhythm
Stage 2	S2 (ROSC)	ROSC at hospital handover	gender + witness/bystander CPR + aetiology + initial rhythm + witness/bystander CPR*gender + witness/bystander CPR*aetiology + witness/bystander CPR*initial rhythm + aetiology*initial rhythm
	S2 (Survival)	Survival to hospital discharge	age + gender + witness/bystander CPR + aetiology + initial rhythm + witness/bystander CPR*gender + witness/bystander CPR*aetiology + witness/bystander CPR*initial rhythm + aetiology*initial rhythm
Stage 3	S3 (ROSC)	ROSC at hospital handover	gender + witness/bystander CPR + aetiology + initial rhythm + witness/bystander CPR*gender + witness/bystander CPR*aetiology + witness/bystander CPR*initial rhythm + aetiology*initial rhythm
	S3 (Survival)	Survival to hospital discharge	age + gender + witness/bystander CPR + aetiology + initial rhythm + witness/bystander CPR*gender + witness/bystander CPR*aetiology + witness/bystander CPR*initial rhythm + aetiology*initial rhythm

Note: *, interaction of two effects. There was no model term dropped from Stage 2 to 3.

Table 4: Discrimination and calibration of the predictive models for ROSC at handover and survival to hospital discharge.

			Model fit	**Discrimination**	**Calibration**			
			AIC	**AUC (95% CI)**	**HL p-value**	**Cox calibration**		**Brier score**
						Intercept	**Slope**	
ROSC	Model S1	2014	18220.0	0.69 (0.68, 0.70)	<0.001	0.00 (-0.05, 0.06)	1.00 (0.95, 1.06)	0.185
		2015	-	0.66 (0.66, 0.67)	<0.001	0.12 (0.06, 0.17)	0.91 (0.85, 0.96)	0.197
	Model S3	2014	18050.2	0.70 (0.69, 0.71)	<0.001	0.00 (-0.05, 0.06)	1.00 (0.95, 1.05)	0.182
		2015	-	0.67 (0.66, 0.68)	<0.001	0.09 (0.03, 0.14)	0.88 (0.83, 0.93)	0.194
Survival	Model S1	2014	6256.1	0.85 (0.84, 0.86)	<0.001	0.00 (-0.09, 0.10)	1.00 (0.95, 1.05)	0.087
		2015	-	0.86 (0.85, 0.87)	<0.001	-0.10 (-0.19, -0.01)	1.01 (0.97, 1.06)	0.072
	Model S3	2014	6208.8	0.85 (0.84, 0.86)	<0.001	0.00 (-0.09, 0.10)	1.00 (0.95, 1.05)	0.086
		2015	-	0.87 (0.86, 0.88)	<0.001	-0.13 (-0.22, -0.05)	1.00 (0.96, 1.05)	0.072

Note: AIC, Akaike information criterion (not reported in the validation): a lower value indicates a better fit. AUC, area under the curve: 1) ≥0.9 = outstanding; 2) 0.8-0.9 = excellent; 3) 0.7-0.8 = acceptable, 4) <0.7 = poor. HL, Hosmer-Lemeshow: p<0.05 suggests poor calibration. Cox calibration: a line with an intercept of 0 and slope of 1 indicates perfect agreement. Brier score is the mean squared error of the predictions and a value of 0 indicates the best prediction. Model S2 included the same main and interaction effects as Model S3 for both outcomes. Hence, the prediction performance summary for Model S2 was omitted.

Figures

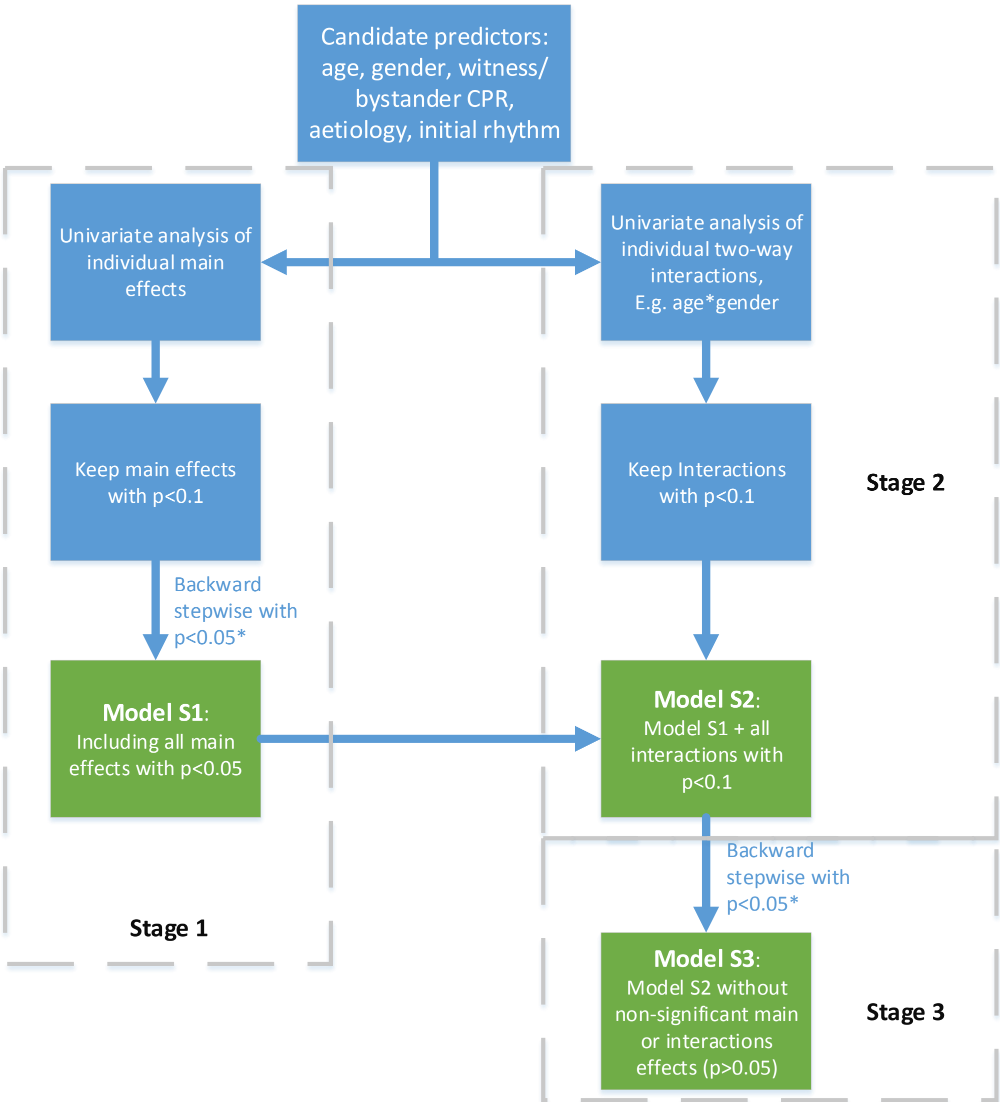

Figure 1: Model development flowchart

*Note: *, non-significant main effect or interaction is removed unless the removal led to poorer model performance.*

ROSC at handover

Survival at discharge

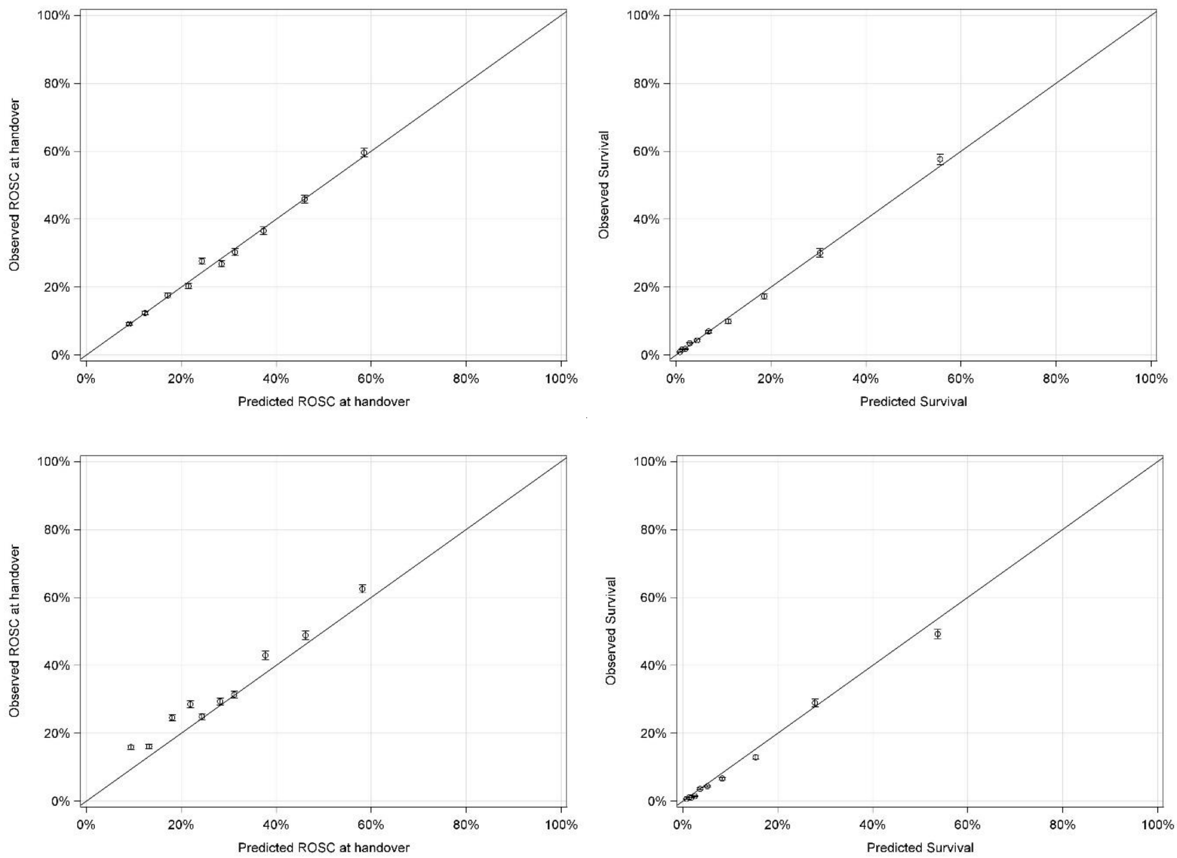

Figure 2: Hosmer-Lemeshow calibration plot of the development (top) and validation data (bottom) for ROSC at handover and survival to discharge (Note: Circles and bars are the observed proportions and 95% confidence intervals of achieved ROSC and survived to discharge in the deciles of predictions)

ABSTRACT

Introduction: The Out-of-Hospital Cardiac Arrest (OHCA) Outcomes project is a national research registry. One of its aims is to explore sources of variation in OHCA survival outcomes. This study reports the development and validation of risk prediction models for return of spontaneous circulation (ROSC) at hospital handover and survival to hospital discharge.

Methods and results: The study included OHCA patients who were treated during 2014 and 2015 by emergency medical services (EMS) from 7 English National Health Service ambulance services. The 2014 data were used to identify important variables and to develop the risk prediction models, which were validated using the 2015 data. Model prediction was measured by area under the curve (AUC), Hosmer-Lemeshow test, Cox calibration regression and Brier score. All analyses were conducted using mixed effects logistic regression models. Important factors included age, gender, witness/bystander cardiopulmonary resuscitation (CPR) combined, aetiology and initial rhythm. Interaction effects between witness/bystander CPR with gender, aetiology and initial rhythm and between aetiology and initial rhythm were significant in both models. The survival model achieved better discrimination and overall accuracy compared with the ROSC model (AUC=0.86 vs 0.67, Brier score=0.072 vs 0.194, respectively). Calibration tests showed over- and under-estimation for the ROSC and survival models, respectively. A sensitivity analysis individually assessing Index of Multiple Deprivation scores and location in the final models substantially improved overall accuracy with inconsistent impact on discrimination.

Conclusion: Our risk prediction models identified and quantified important pre-EMS intervention factors determining survival outcomes in England. The survival model had excellent discrimination.

Appendix

Appendix Table 1: Calibration, discrimination and overall accuracy of the sensitivity analysis

			AUC (95% CI)	HL p-value	Cox calibration		Brier score
					Intercept	Slope	
ROSC	Model S3 + IMD 2010	2014	0.77 (0.76, 0.78)	0.001	0.00 (-0.07, 0.08)	1.00 (0.94, 1.06)	0.066
		2015	0.68 (0.66, 0.69)	0.891	0.50 (0.43, 0.57)	0.60 (0.54, 0.66)	0.074
	Model S3 + IMD 2015	2014	0.77 (0.76, 0.78)	0.001	0.00 (-0.07, 0.08)	1.00 (0.94, 1.06)	0.066
		2015	0.68 (0.66, 0.69)	0.953	0.50 (0.43, 0.57)	0.60 (0.54, 0.66)	0.074
	Model S3 + location	2014	0.71 (0.70, 0.72)	<0.001	0.00 (-0.07, 0.08)	1.00 (0.93, 1.08)	0.082
		2015	0.65 (0.63, 0.68)	0.001	0.51 (0.34, 0.68)	0.74 (0.61, 0.87)	0.032
Survival	Model S3 + IMD 2010	2014	0.89 (0.87, 0.90)	<0.001	0.00 (-0.12, 0.13)	1.00 (0.93, 1.07)	0.035
		2015	0.83 (0.82, 0.85)	<0.001	-0.19 (-0.29, -0.08)	0.82 (0.76, 0.88)	0.034
	Model S3 + IMD 2015	2014	0.89 (0.87, 0.90)	<0.001	0.00 (-0.12, 0.13)	1.00 (0.93, 1.07)	0.035
		2015	0.83 (0.82, 0.85)	0.881	-0.18 (-0.29, -0.08)	0.82 (0.76, 0.89)	0.034
	Model S3 + location	2014	0.85 (0.84, 0.87)	<0.001	0.00 (-0.12, 0.13)	1.00 (0.93, 1.08)	0.039
		2015	0.84 (0.81, 0.87)	0.030	-0.76 (-0.95, -0.57)	0.88 (0.75, 1.02)	0.009

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